Trends Journal of Sciences Research, 2018, Volume 3, Issue 2, 75-81
http://www.tjsr.org/journal/index.php/tjsr
DOI: 10.31586/Nursing.0302.03

Lifestyle Management Still Relevant, Despite Genetics Advancement, in Non-Communicable Diseases Risks: A Perspective

Prince Chikwere[1,*], Ishawu Iddrisu[2]

[1]Department of Nursing, All Nations University College, Ghana
[2]Department of Biochemistry and Biotechnology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
*Corresponding author: uc.princechik@gmail.com

Mini Review

Open Access

How to cite this article: Chikwere, P., & Iddrisu, I. (2018). Lifestyle Management Still Relevant, Despite Genetics Advancement, in Non-Communicable Diseases Risks: A Perspective. *Trends Journal Of Sciences Research, 3*(2), 75-81.
https://doi.org/10.31586/Nursing.0302.03

Received: August 01, 2018

Accepted: September 05, 2018

Published: September 07, 2018

Copyright © 2018 by authors and Trends in Scientific Research Publishing.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/

Abstract Genotype and lifestyle factors have been implicated as the causes of non-communicable diseases including diabetes, cardiovascular diseases, cancer and chronic respiratory disease. Lifestyle factors constitute physical activity, smoking, alcohol intake and dietary habits. These factors alongside genetic factors have been studied over the past years on their relationships with non-communicable diseases. This review examined and compared the strengths of the two factors, lifestyle and genotype, in causing non-communicable diseases. A search was done online, predominantly with PubMed, to identify articles that contained the keywords, lifestyle, diet, exercise, genotype, gene, non-communicable diseases, cardiovascular diseases, cancer, chronic respiratory disease, diabetes. For diabetes, the results of this review showed that management of lifestyle factors can be used to prevent type 2 diabetes among genetically predisposed persons. Cancers studies have suggested that a Mediterranean diet is associated with lower cancer risk for both genetically susceptible people and non-susceptible individuals. Similar findings were gotten for cardiovascular diseases and chronic respiratory diseases. The results suggest a strong impact of lifestyle-related factors as a cause of non-communicable diseases though genetic factors cannot be underestimated. With good management of lifestyle factors, non-communicable diseases can be prevented and the risks reduced even among genetically high-risk individuals.

Keywords: *Lifestyle, Genes, Non-Communicable Diseases, Perspective*

1. Introduction

Non-communicable diseases (NCDs), as the name implies, are non-infectious diseases or chronic conditions, for which complete cure is rarely achieved. Types of NCDs, though not exhaustive, include cardiovascular diseases, cancer, chronic respiratory disease, diabetes, chronic neurological disorders, and arthritis. According to World Health Organisation (WHO), cardiovascular diseases, cancer, chronic respiratory disease, and diabetes are the 4 main types of NCDs [1]. These 4 main NCDs will be considered in this review.

Lifestyle and genes have been studied for their role in the prevention, development and advancement of NCDs. Lifestyle which constitutes modifiable risk factors involves, physical inactivity, alcohol misuse, smoking (tobacco use), and unhealthy diet [1], and non-modifiable risk factors include age, gender, race, and family history /genetics. A study by Melaku *et al.* [2] sought to find the trend of disease burden related to dietary risks between 1990 to 2013 in Ethiopia. A 61.2% increase in number of deaths caused by NCDs associated with poor diet was recorded in 2013, with reference

to 1990. Intake of sugar was associated with a lower risk of the metabolic syndrome among the A allele carriers of rs670, T allele carriers of rs5069, the apoA1combined GA+AA/CT+ TT/CC genotypes. Also, higher metabolic risk was recorded among participants of GG genotypes (at apoA1 expression site rs670) who had high nuts intakes compared with those with minor allele carriers who had low nuts intakes [3]. Apolipoprotein A1 (apoA1) is a major structural and functional protein constituent of HDL-cholesterol. Dietary intakes and nutrients exert individual effects in the concentrations of biochemical indices; this biochemical difference can be attributed to variables in genetic predisposition. Genome-wide association studies, for more than a decade are being used to identify genes involved in human disease.

The need for personalised nutrition has been emphasised as genetic variation for metabolic diseases is prevalent among individuals and populations. Genetic variants at various loci have been associated with increased risk of many diseases. This review sought to compare the strength of the two factors: lifestyle and gene, in the prevention and management of NCDs. The results of this review are not intended to undermine the role of one factor nor overestimate the role of the other in disease control.

2. Non-Communicable Diseases and Genes and Lifestyle

2.1. Diabetes

Diabetes is a metabolic disease condition characterised by high blood glucose due to an inability to produce insulin, or inability to metabolise sufficient quantities of the hormone. By the definition, diabetes exists in two types: type 1 diabetes (referred to as insulin-dependent diabetes mellitus and type 2 diabetes called non-insulin dependent diabetes mellitus). Lifestyle is generally seen as a major factor in type 2 diabetes. Several studies have suggested that management of lifestyle factors can be used to prevent type 2 diabetes and its complications. Lifestyle management could be very good in preventing and managing dyslipidaemia in type 2 diabetes patients [4]. Even high exercise intensity has been associated with improved cardiovascular risk factors in type 2 diabetes patients [5]. Type 2 diabetes is thus a lifestyle-related condition.

Various dietary habits and patterns have been related to type 2 diabetes and/or its complications. Naicker *et al.* [6] identified two dietary patterns, with reference to percentage fat supplies by the food groups considered, in an Indian population living in South Africa. The "Meat and fish versus legume and cereal" pattern, described as "added fat" pattern, was associated with increased NCD risk among the Indians. However, the "nuts and seeds versus sugar and fat" pattern was considered a healthy pattern. In a similar study conducted in Ghana [7], 'Processed, Meat and Legumes' dietary pattern, characterised by high consumption of meat, cereals, legumes, milk and other processed foods, fruits, and tea, was associated with high lipid levels. The 'Vegetables and Fish' dietary pattern was considered healthy as it was associated with low lipid levels. Even 'Grains, Fried and Salted' dietary pattern was associated with low serum uric acid. Dietary patterns vary based on availability of foods, the place and cultural origin under study [4], and the impact of the foods may be influenced by genetic factors. Phenotypical differences exist as a result of the interplay between variant genetic factors and different environmental factors (including lifestyle). Interaction between genetic factors and lifestyle factors has been postulated, many years ago, to cause type 2 diabetes and not either of them alone [8], and recently buttressed in a large European study [9]. Similarly, Langenberg *et al.* [10] found that obese individuals were genetically predisposed to type 2 diabetes.

The effects of genetic risk cannot be overlooked in type 2 diabetes. Younger individuals and leaner persons are not genetically susceptible to type 2 diabetes as compared to their older and fatter (in terms of Body Mass Index and Waist Circumference) counterparts [10]. Sugar and sweet beverages intakes interacted with combined apoA1/ apoC3 genotypes on metabolic risk. Higher metabolic risk was observed among individuals with combined GA+AA/CT+TT/CC genotypes who took sugar and sweet beverages or fish. In a study by Walker *et al.* [11], lifestyle had a greater influence in glycaemic control than genetic composition. Improved insulin sensitivity and glycaemic control were linked to paths of lifestyle factors improvement, in contrast to the type 2 diabetes genetic predisposition score which only showed influence when lifestyle factors were considered. In another study, the interaction of genes with nutrients for the development and progression of the disease was examined [12]. The effect of nutrigenetics has been demonstrated in the

pathogenic pathway of type 2 diabetes. Hivert *et al.* [13] studied the relation of genes with type 2 diabetes risks in a multi-ethnic setting. Subjects who had higher type 2 diabetes genetic susceptibility were more likely to become type 2 diabetes patients. Genetic susceptibility to type 2 diabetes was associated with reduced ability to return to normal glucose levels once hyperglycaemia sets in. However, lifestyle modification improved the outcome in the high-risk subjects. Though genomics may be important in understanding the pathophysiology of type 2 diabetes, the role of nutrition and other lifestyle factors is still significant in public health.

2.2. Cancer

Cancer is a disease condition in which the cells of a tissue undergo proliferative uncontrolled growth. As oncology advances, the pathophysiology of cancer cells continues to be a major concern of researchers. Food choices as well as genes are contributory factors to cancer risks. Individual foods, dietary patterns and lifestyle have been investigated for their role in various cancer risks or overall cancer risks. The genetic disposition of individuals has also been studied as a predisposing factor in cancers.

Functional foods and the active substances in these foods reduce risks for various cancers [14]. In a European study, Mediterranean diet was associated with risk of gastric adenocarcinoma [15]. Compared to those who had low consumption, those who highly stuck to Mediterranean diet had lower risk of gastric adenocarcinoma. Though not significant, even individuals who highly adhered to Mediterranean diet (but smoked) had a reduced risk for gastric adenocarcinoma. Food plays significant role in the pathway of cancer development and progression. A study conducted in Spain showed lifestyle has a greater strength than genes in colorectal cancer risks [16]. Individuals with family history of colorectal cancer had greater genetic susceptibility to the chronic condition. Also both lifestyle factors (high consumption of alcohol, obesity, lack of physical activity, high intake of red meat, and low intake of vegetables) and genes had independent association with colorectal cancer risk but the lifestyle exhibited five times greater risk. Thus, changes in lifestyle, such as achieving a healthy weight or consuming less meat and more vegetables, influence cancer risk more than genetics. Obesity is a major lifestyle factor because of its association with unhealthy diet and physical inactivity; it has been associated with colorectal cancer [17]. Lifestyle and obesity management is very important in the prevention of colorectal cancer.

In a case-control study, some genetic variants (*ARL11, ADH1C, GALNTL2* and *IL6*) were suggested to have an effect on colorectal neoplasm risk [18]. Other Single Nucleotide Polymorphisms have been investigated for genetic susceptibility to colorectal cancers. Genome-wide association studies have been conducted in various populations to identify susceptibility loci. However, these identified loci might not work for other populations or ethnic groups, as extrapolation may not be possible. Susceptibility loci of breast cancer located in population of European decent did not work for women of African ancestry [19]. Genome-wide association studies should cover many more ethnic groups in order to find the variants responsible for this NCD in many parts of the globe. Identifying individuals who are genetically susceptible to cancer is important for knowledge of the genetically high-risk population. This will buttress the need to intensify lifestyle education among the high-risk persons. A study by Ko *et al.* [20] associated high meat consumption independently with breast cancer risk in BRCA (BReast CAncer gene) mutation carriers and non-carriers. However, the carriers were at greater risk (Hazard Ratio of 1.97) compared to the non-carriers (Hazard ratio of 1.41). Also, subjects who consumed soy products and vegetables had a lower risk of breast cancer; high soy products reduced the risk of breast cancer even in BRCA mutation carriers. Notably, BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins; inherited mutations of these genes increase the risk of breast cancer.

It is important that individuals, especially already genetically susceptible persons, prevent modifiable factors including various lifestyle that predispose them to breast cancer or other cancers. Diet is very important in the prevention of cancers. Even Mediterranean diet supplemented with either olive oil or nuts prevented breast cancer in adult women (60-80 years) at high risk of cardiovascular disease [21]. The olive oil-supplemented diet showed a greater protection against breast cancer in this study. Exercise was associated with lower risk of polyps (abnormal tissue growth) and colorectal cancer in a multi-ethnic study in the US [22]. Exercise was more efficient in the obese and overweight subjects, and even in high-risk ethnic groups in reducing risk for polyps and the cancer.

2.3. Cardiovascular disease

Cardiovascular disease is an abnormal condition of the heart and/or the blood vessels. Genetic susceptibility to cardiovascular disease is notable; even genetic risk variants have been associated with nearby genes in the pathogenesis of the NCD [23]. Among Hispanic/Latino adults, lifestyle risk factors and genetics were independently and together associated with myocardial infarction [24]. However, lifestyle risk factors were more strongly associated with myocardial infarction. Sotos-Prieto *et al.* [24] suggested that efforts should be to improve lifestyle irrespective of genotype in order to prevent cardiovascular diseases. In a recent study, Corella *et al.* [25] investigated the association between the Circadian Locomotor Output Cycles Kaput (CLOCK) gene and the incidence of type 2 diabetes and cardiovascular diseases in type 2 diabetic subjects. They also looked at how this association can be modulated by diet. The study was a longitudinal one and participants were followed for a median of 4.8 years and the incidence of type 2 diabetes and cardiovascular diseases were assessed as a primary outcome. The results showed an association between the CLOCK gene and a lower incidence of type 2 diabetes. However, the study reported an association between the CLOCK gene polymorphism and stroke in type 2 diabetic subjects hence these genes may contribute significantly to increased risk of cardiovascular diseases in type 2 diabetics [25]. Also, mutation in the NOTCH1 (signaling and transcriptional regulator) has been associated with the development of the aortic valve disease [26].

Of course, Khera *et al.* [27] found a "favourable lifestyle" to reduce risk of coronary disease by about half in individuals at high genetic risk of the NCD. Interestingly, the lower the genetic risk, the lower the relative risk of the disease association with favourable lifestyle, compared to unfavourable lifestyle. Khera *et al.* [27] defined favourable lifestyle as 'no current smoking', 'no obesity', 'regular physical activity', and 'healthy diet'. Intakes of certain foods and nutrients therein have been associated with deaths from heart disease and stroke [28]. Individuals have to be mindful of the types of foods/nutrients they take and their proportions relative to other foods. Mediterranean diets, which have been generally linked to prevention of cardiovascular diseases, have been associated with reduced risk of cardiovascular disease even in high-risk individuals [29]. Such Mediterranean diet was however fortified with either extra-virgin olive oil or nuts. The high-risk individuals were either type 2 diabetes patients or had any three of the following: smoking, hypertension, high low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature coronary heart disease. Interestingly, the subjects in the study were adults aged between 55-80 years, which is by itself a risk factor. A healthy dietary pattern with good lifestyle can prevent progression to a cardiovascular disease even in adults who are at risk of the condition.

2.4. Chronic respiratory disease

Chronic respiratory disease affects the airways, including the lungs as well as the passages and structures associated with the lungs. This disease includes, though not exhaustive, chronic obstructive pulmonary disease (COPD), asthma, pulmonary hypertension, bronchiectasis, chronic sinusitis, sleep apnoea syndrome and occupational lung disease.

An European study identified three dietary patterns: the "cosmopolitan" pattern (characterised by high intakes of vegetables, fish, chicken, wine, rice and lower intakes of high-fat dairy products, added fat, added sugar, and potato), the "traditional" pattern (characterised by high intakes of red meat, processed meat, potato, boiled vegetables, added fat, coffee, and beer and lower intakes of soy products, low-fat dairy products, tea, breakfast cereal, brown rice, pizza, juice, and fruit), and the "refined food" pattern (characterised by high intakes of mayonnaise, salty snacks, candy, high-sugar beverages, French fries, white bread, and pizza and lower intake of boiled vegetables, wholegrain bread, fruit, and cheese [30]. High intake of any of the 3 dietary patterns was associated with poor lung function and COPD, wheeze, or asthma. These associations were however not consistent through the quintiles of consideration in the study. It is therefore unclear whether modification of diet could ameliorate chronic respiratory disease risk or not. However, it is clear that the associations found between the dietary patterns and the poor respiratory health conditions were significant comparing persons in the first quintile to those in the fifth quintile of the dietary patterns. Thus, respiratory disease might not be associated with the level of intakes or conform to any of these dietary patterns, but a very high intake of a dietary pattern may be deleterious to subjects involved.

A multi-ethnic study in the US found that smokers, irrespective of their ethnic group, have increased risk of poor respiratory health (decreased lung function and emphysema) [31]. The genotype and the ethnicity of the subjects had no significant influence in this association. This makes cigarette smoking an important modifiable factor in respiratory health regardless of an individual's ethnic group or genetic ancestry. Smoking cessation might not be the single most important intervention in promoting good respiratory health. Smokers with high alcohol intake or high "westernised" dietary pattern were more likely to develop poor lung function [32]. However, smokers who had high "Mediterranean-like" dietary pattern intake were less likely to have poor lung function. Subjects in this study were Spanish with no known respiratory disease. The "westernised" dietary pattern was characterised by high meats, dairy products, and sugary drinks, sweets, and low fruits, vegetables, legumes, and fish, while the "Mediterranean-like" dietary pattern was high in poultry, eggs, fish, vegetables, legumes, potatoes, dairy desserts, fruits, nuts, and dried fruit.

It will be misconstruing to suggest that genotype is not important in ameliorating chronic respiratory disease. Molecular genetics gives a clearer understanding of the pathophysiology of diseases. It elucidates the epidemiology and even inheritance of diseases. Even certain genetic loci are implicated in different diseases. Degree of lung function, coronary artery disease risk and carotid intima-media thickness were controlled by same genes [33].

3. Conclusion

It is prudent for preventive care against NCDs to be targeted mainly on lifestyle. Major modifiable risk factors including tobacco use, alcohol consumption, physical activity, and diet are considered manageable and exhibit great potential in the reduction of NCD burden. Genetic predisposition is very important in that it gives understanding of the populations at high risk of one NCD or the other who must receive greater attention in terms of lifestyle intervention. Thus nutrition in particular, should be tailored towards molecular individuality for the prevention of NCDs. However, it will not be a prudent preventive measure to ignore genetically less-susceptible individuals or populations. Although the extent of protection may be conferred by genetic background, lifestyle should be used as a preventive measure to reduce risk of NCDs for the promotion of Finally, irrespective of genetic predisposition, lifestyle intervention should be intensified to reduce the global burden of NCDs.

References

[1] World Health Organisation, Global action plan for the prevention and control of non-communicable diseases 2013-2020. Available at: who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf. 2013. Accessed March 22, 2017.

[2] Melaku YA, Temesgen AM, Deribew A, Tessema GA, Deribe K, Sahle BW, *et al.* The impact of dietary risk factors on the burden of non-communicable diseases in Ethiopia: findings from the Global Burden of Disease study 2013. *International Journal of Behavioral Nutrition and Physical Activity* 13 (2016) 122-134.

[3] Hosseini-Esfahani F, Mirmiran P, Daneshpour MS, Mottaghi A, Aziz F. The effect of interactions of Single Nucleotide Polymorphisms of APOA1/APOC3 with food group intakes on the risk of metabolic syndrome. *Avicenna J Med Biotech* 9 (2017) 94-103.

[4] Chikwere P, Annan RA. Dietary habit and other lifestyles and serum lipid profile of type 2 diabetes patients: a systematic review. *Nutrition & Food Science* 46 (2016) 161-170.

[5] Chikwere P, Nsiah K, Tandoh MA. Relation of unsupported and unsupervised exercise with anthropometric and biochemical indices among type 2 diabetic patients. *Turk J Med Sci* 47 (2017) 85-90.

[6] Naicker A, Venter CS, MacIntyre, UE, Ellis S. Dietary quality and patterns and non-communicable disease risk of an Indian community in KwaZulu-Natal. *South Africa Journal of Health, Population and Nutrition* 33 (2015) 12-20.

[7] Chikwere P, Nsiah K, Tandoh MA, Agyenim-Boateng K. The relation of dietary pattern to serum lipid profile and uric acid among type 2 diabetes patients. *J. Nutr. Ecol. Food Res* 2 (2014) 207-213.

[8] Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 14 (1962) 353-362.

[9] Langenberg C, Sharp S, Forouhi NG, Franks P, Schulze MB, Kerrison N, *et al.* The InterAct Project: An Examination of the Interaction of Genetic and Lifestyle Factors on the Incidence of Type 2 Diabetes in the EPIC Study. *Diabetologia* 54 (2011) 2272-2282.

[10] Langenberg C, Sharp SJ, Franks PW, Scott RA, Deloukas P, Forouhi NG, *et al.* Gene-lifestyle interaction and type 2 diabetes: The EPIC InterAct case-cohort study. *PLoS Med* 11 (2014) e1001647.

[11] Walker CG, Solis-Trapala I, Holzapfe C, Ambrosini GL, Fuller NR, Loos RJF, *et al.* Modelling the interplay between lifestyle factors and genetic predisposition on markers of type2 diabetes mellitus risk. *PLoS ONE* 10 (2015) e0131681.

[12] Phillips CM. Nutrigenetics and metabolic disease: current status and implications for personalised nutrition. *Nutrients* 5 (2013) 32-57.

[13] Hivert M, Jablonski KA, Perreault, L. Updated genetic score based on 34 confirmed type 2 diabetes loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. *Diabetes* 60 (2011) 1340-1348.

[14] Chikwere P. Functional foods and nutraceuticals, wonders in cancer risks - a review. *World Scientific News* 64 (2017) 18-33.

[15] Buckland G, Agudo A, Luján L, Jakszyn P, Bueno-de-Mesquita H, Palli D, *et al.* Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr* 91 (2010) 381-390.

[16] Ibáñez-Sanz G, Díez-Villanueva A, Henar Alonso M, Rodríguez-Moranta F, Pérez-Gómez B, Bustamante M, *et al.* Risk Model for Colorectal Cancer in Spanish Population Using Environmental and Genetic Factors: Results from the MCC-Spain study. *Scientific Reports* 7 (2017) 43263.

[17] Stein B, Anderson JC, Rajapakse R, Alpern ZA, Messina CR, Walker G. Body mass index as a predictor of colorectal neoplasia in ethnically diverse screening population. *Dig Dis Sci* 55 (2010) 2945-2952.

[18] Abulí A, Fernández-Rozadilla C, Alonso-Espinaco V, Muñoz J, Gonzalo V, Bessa X, *et al.* Case-control study for colorectal cancer genetic susceptibility in EPICOLON: previously identified variants and mucins. *BMC Cancer* 11 (2011) 339-346.

[19] Huo D, Zheng Y, Ogundiran TO, Adebamowo C, Nathanson KL, Domchek SM, *et al.* Evaluation of 19 susceptibility loci of breast cancer in women of African ancestry. *Carcinogenesis* 33 (2012) 835–840.

[20] Ko K-P, Kim S-W, Ma SH, Park B, Ahn Y, Lee JW, *et al.* Dietary intake and breast cancer among carriers and noncarriers of BRCA mutations in the Korean Hereditary Breast Cancer Study. *Am J Clin Nutr* 98 (2013) 1493-1501.

[21] Toledo E, Salas-Salvadó J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E, *et al.* Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial: A Randomized Clinical Trial. *JAMA Intern Med* 175 (2015) 1752-1760.

[22] Sanchez NF, Stierman B, Saab S, Mahajan D, Yeung H, Francois F. Physical activity reduces risk for polyps in a multiethnic colorectal cancer screening population. *BMC Research Notes* 5 (2012) 312-319.

[23] Folkersen L, van't Hooft F, Chernogubova E, Agardh HE, Hansson GK, Hedin U. Association of genetic risk variants with expression of proximal genes identifies novel susceptibility genes for cardiovascular disease. *Circ Cardiovasc Genet* 3 (2010) 365-373.

[24] Sotos-Prieto M, Baylin A, Campos H, Qi L, Mattei J. Lifestyle Cardiovascular Risk Score, Genetic Risk Score, and Myocardial Infarction in Hispanic/Latino Adults Living in Costa Rica. *J Am Heart Assoc* 5 (2016) e004067.

[25] Corella D, Asensio EM, Coltell O, Sorlí, J. V., Estruch, R., Martinez-González, M.A, *et al.* CLOCK gene variation is associated with incidence of type 2 diabetes and cardiovascular diseases in type 2 diabetic subjects: dietary modulation in the PREDIMED randomized trial. *Cardiovascular Diabetology* 15 (2016) 4-15.

[26] Garg V, Muth AN, Ransom JF, Schluterman MK, Barnes R, King IN, *et al.* Mutation in NOTCH1 cause aortic valve disease. *Nature* 437 (2005) 270-274.

[27] Khera AV, Emdin CA, Drake I. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med* 375 (2016) 2349-2358.

[28] Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA* 317 (2017) 912-924.

[29] Estruch R, Ros E, Salas-Salvadó J. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med* 368 (2013) 1279-1290.

[30] McKeever TM, Lewis SA, Cassano PA, Ocké M, Burney P, Britton J, Smit HA, *et al.* Patterns of dietary intake and relation to respiratory disease, forced expiratory volume in 1 s, and decline in 5-y forced expiratory volume. *Am J Clin Nutr* 92 (2010) 408-415.

[31] Powell R, Davidson D, Divers J, Manichaikul A, Jeffrey Carr J, Detrano R, *et al.* Genetic ancestry and the relationship of cigarette smoking to lung function and per cent emphysema in four race/ethnic groups: a cross-sectional study. *Thorax* 68 (2013) 634-642.

[32] Sorli-Aguilar M, Martin-Lujan F, Flores-Mateo G, Arija-Val V, Basora-Gallisa J, Sola-Alberich R. Dietary patterns are associated with lung function among Spanish smokers without respiratory disease. *BMC Pulmonary Medicine* 16 (2016) 162-173.

[33] Sabater-Lleal M, Mälarstig A, Folkersen L, Artigas MS, Baldassarre D, Kavousi M, Almgren P, *et al.* Common Genetic Determinants of Lung Function, Subclinical Atherosclerosis and Risk of Coronary Artery Disease. *PLoS ONE* 9 (2014) e104082.